NEW CYCLOALKANEDIONE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL APPLICATIONS

DESCRIPTION

TECHNICAL FIELD OF THE INVENTION

The present invention relates to new chemical compounds, their preparation, pharmaceutical formulations that contain them and their use in medicine, the present invention particularly relating to new cycloalkanedione derivatives which are serotonin (5-hydroxytriptamine, 5-HT) 5-HT_{1A} receptor subtype agonists. Therefore, they are useful in the treatment of pathological states for which an agonist of these receptors is indicated.

In particular, the compounds of the present invention are useful as neuroprotective agents, which confers them a special interest in the treatment and prophylaxis of cerebral damage due to traumatic or ischemic stroke.

BACKGROUND OF THE INVENTION

The pharmacological possibilities for the treatment of acute cerebral stroke are very limited; until now, only thrombolitic therapy using a tissue plasminogen activator (tPA) can be moderately effective. Although the primary cellular damage caused by ischemia is not susceptible to treatment, there is the possibility of acting on secondary neuronal death in the penumbra zone, where a series of processes extending the damage occurs. Amongst them, particular attention has been paid to massive release of excitatory amino acids, and in this sense, drugs that prevent glutamate release, glutamate receptor antagonists, both NMDA and AMPA receptors, are effective in different experimental models.

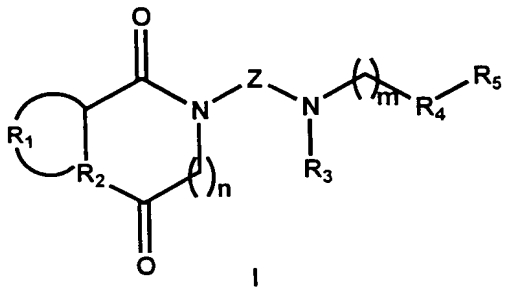
At present, 14 different subtypes of serotonergic receptors are known. The 5-HT_{1A} receptors, the localization

injuries.

DESCRIPTION OF THE INVENTION

The present invention, as indicted in the heading, relates to new cycloalkanedione derivatives, their preparation process and their pharmacological applications.

In a first aspect of the present invention, said cycloalkanedione derivatives are characterized in that they correspond to the general formula I:



I

where:

R_1 is selected from the group formed by H, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH_2-S-CH_2$, $-S-CH_2-CH_2-$;

R_2 is selected from the group formed by N, S;

n has a value of 0 or 1;

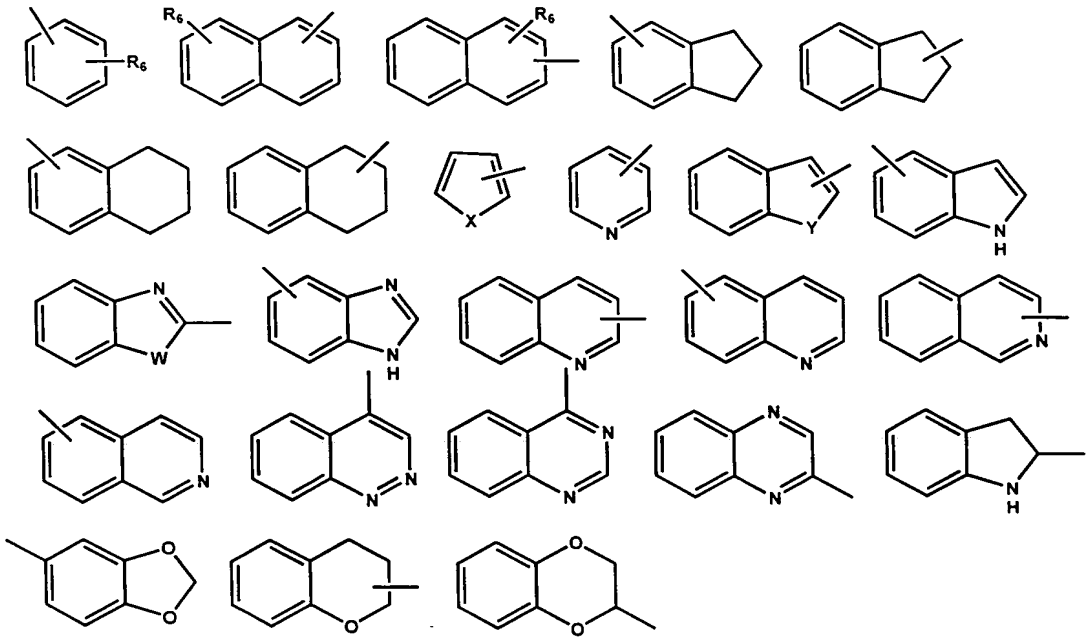
Z is selected from the group formed by C2-C10-alkyl, C2-C10-alkenyl, C2-C10-alkinyl;

R_3 is selected from the group formed by H, C1-C10-alkyl, aryl, aralkyl;

m has a value of 0 to 2;

R_4 is selected from the group formed by O, CH_2;

R_5 is selected from the group formed by:



where:

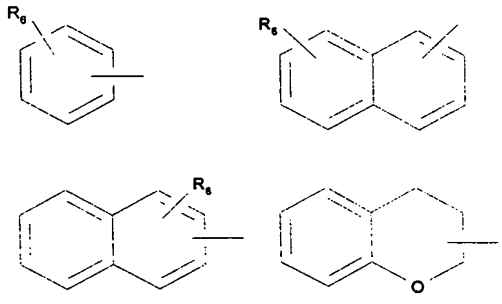
R_6 is selected from the group formed by H, C1-C5-alkyl, C1-C5-alkoxyl, OH, F, Cl, Br, I;

X is selected from the group formed by O, S, NH, NCH_3;

Y is selected from the group formed by O, NH;

W is selected from the group formed by S, NH.

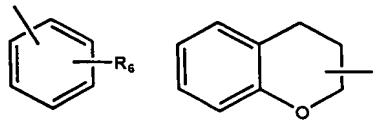
In a preferred embodiment of the present invention, the formula (I) compounds are those where: Z represents a C2-C10-alkyl group, and R_5 is selected from the group formed by:



where the definitions of R_1, R_2, R_3, n, m, R_4 and R_6 are identical to those previously made.

Even more preferred are formula (I) compounds where:

Z is butyl, R_3 is H, and R_5 is selected from the group formed by:



where the definitions of R_1, R_2, n, m, R_4 and R_6 are identical to those previously made.

Unless otherwise indicated, the alkyl groups referred to in the present invention, as well as the alkyl residues of other groups referred to in the present invention (e.g. alkoxyl), can be linear or branched, and can also be cyclic (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), or linear or branched and contain these cyclic residues.

Unless otherwise indicated, the alkenyl groups referred to in the present invention are linear (e.g. 1-propenyl, 2-butenyl) and their isomeric forms.

Unless otherwise indicated, the alkinyl groups referred to in the present invention are linear (e.g. 2-butinyl).

The term aryl includes any monocyclic aromatic group containing between 5 and 12 carbon atoms, optionally interrupted by one or several heteroatoms selected from N, O or S.

The term aralkyl refers to an aryl group bonded to a previously defined alkyl group, such as benzyl or phenethyl.

In the scope of the present invention, the compounds according to the invention may have several asymmetric carbon atoms and, therefore, have various stereochemical forms. The compounds according to the invention may also be in the form of their salts. In general, their salts with inorganic or organic acids can be mentioned.

In the scope of the present invention, those salts which are physically compatible will be preferable.

Particularly preferable are, for example, the salts with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, *o*-toluene sulphonic acid, *m*-toluene sulphonic acid, *p*-toluene sulphonic acid, benzene sulphonic acid, *o*-naphthalene sulphonic acid, *m*-naphthalene sulphonic acid, *p*-naphthalene sulphonic acid, acetic acid, propionic acid, lactic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid or benzoic acid.

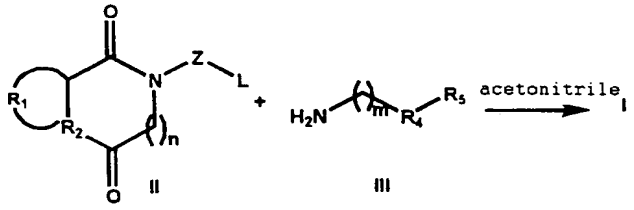
The compounds with potent agonist action on the 5-HT_{1A} receptor disclosed in the present invention represent, therefore, effective products to treat diseases of the central nervous system which include anxiety disorders, different forms of depression and mixed disorders of anxiety-depression such as obsessive compulsive disorders, phobias, bulimia, etc. They are also suitable for prophylaxis and treatment of neuronal damage in episodes of cerebral infarction, in promoting the survival of cells located in the penumbra zone surrounding the ischemic focus.

The new active products can be transformed in a known manner in usual formulations, such as tablets, coated tablets, capsules, pills, granulates, micro-granules, aerosols, syrups, emulsions, suspensions and solutions, with the use of pharmaceutically suitable, non-toxic, inert excipients or solvents. In this case, the therapeutically active compound should be present in a concentration of approximately 0.5 to 90% by weight of the total mixture, i.e. in sufficient quantities to attain the indicated dosage range.

The compounds herein disclosed are pure serotonergic 5-HT_{1A} receptor agonists, which have been demonstrated by appropriate functional studies. Consequently, the compounds

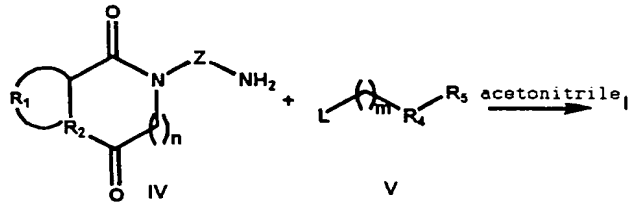
subject of the present invention have a protective effect on the neuronal death of an apoptotic or necrotic character induced by serum deprivation or by glutamate in neuronal cultures.

According to another aspect of the present invention, two alternative processes are provided to prepare the compounds of general formula I: by reaction of intermediate halogen derivatives II (L = Cl, Br) with suitable amines III in acetonitrile as reaction solvent (Scheme I below), or by reaction of intermediate amines IV with appropriate halogen derivatives V (L = Cl, Br) in acetonitrile as reaction solvent (Scheme II below).



II III

Scheme I



IV V

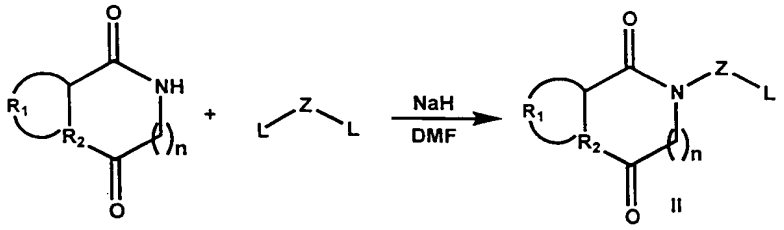
Scheme II

The compounds with R_3 different from H are produced by alkylation of the analogues wherein R_3 is hydrogen.

The definitions of R_1, R_2, n, Z, m, R_4 and R_5 in these schemes are identical to those made previously for the products of the invention.

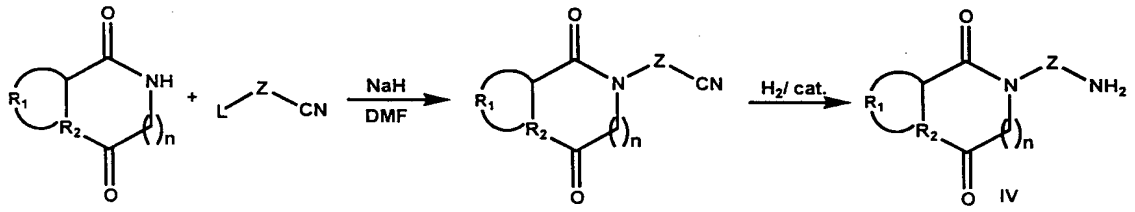
The formula II intermediates are obtained by the reaction of hydantoin, diketopiperazine or cyclic imide with the appropriate halogen derivative in the presence of

sodium hydride and N,N-dimethylformamide as a reaction solvent, as represented in Scheme III.



Scheme III

The formula IV intermediates are obtained by reaction of hydantoin, diketopiperazine or cyclic imide with the appropriate halonitrile in the presence of sodium hydride and N,N-dimethylformamide as reaction solvent, and subsequent catalytic hydrogenation, as represented in Scheme IV.



Scheme IV

Some of the intermediates III and V are commercial. It is also possible to obtain said intermediates following procedures disclosed in the literature or by conventional synthetic routes.

The final products have been structurally characterized by techniques of IR, NMR and quantitative elemental analysis. For easier handling, when the final product is not crystalline it is transformed in a pharmaceutically acceptable salt, derived from an inorganic or organic acid.

The *in vitro* affinity of the compounds of general

formula I in the 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, 5-HT_4, 5-HT_7, α_1 and D_2 cerebral receptors have been evaluated by radioligand displacement tests. The following specific ligands and tissues have been used:

(a) 5-HT_{1A} receptors, [^{3}H]-8-OH-DPAT, rat cerebral cortex;

(b) 5-HT_{2A} receptors, [^{3}H]ketanserin, rat cerebral cortex;

(c) 5-HT_3 receptors, [^{3}H]LY 278584, rat cerebral cortex;

(d) 5-HT_4 receptors, [^{3}H]GR 113808, rat striatum;

(e) 5-HT_7 receptors, [^{3}H]-5-CT, rat hypothalamus;

(f) α_1 receptors, [^{3}H]prazosin, rat cerebral cortex;

(g) D_2 receptors, [^{3}H]spiperone, rat striatum.

The functional character (agonist/antagonist) of the compounds of the present invention, has been studied *in vitro* by determining the inhibition of the stimulating effect of forskolin on adenylate cyclase in a cell line transfected with the 5-HT_{1A} receptor, occasionally comparing the effect obtained with the [^{35}S]GTPγS fixation test to coronal sections of rat brain as well as the hyperpolarizing effect in the hippocampal area CA1, and further studying, *in vivo*, the 5-HT_{1A} agonist character of the new compounds by analysis of the typical behavioural effects as well as of the hypothermia, and evaluating the prevention of these effects by the selective antagonist WAY-100635.

Furthermore, the neuroprotective activity of the compounds disclosed in the present invention has been studied, considering their capacity to prevent cell death, of a necrotic or apoptotic nature, in primary neuronal cultures and studying *in vivo* the prevention of neuronal death in the hippocampal area CA1 of gerbils after

transient global ischemia as well as the reduction in volume of cerebral infarction after permanent occlusion in the middle cerebral artery in rats.

The present invention is illustrated with the following non-limitative examples.

EXAMPLES

EXAMPLE 1: Synthesis of the compounds of general formula I. General process.

To 1.5 mmol of intermediate amine III or IV dissolved in 2 mL of acetonitrile, a solution of 1.0 mmol of halogen derivative II or V in 1.5 mL of acetonitrile is added dropwise. The reaction mixture is heated to 60°C with stirring during 6-24 hours (t.l.c.). After cooling, the solvent is removed at reduced pressure, the residue is dissolved in methylene chloride (20 mL) and is washed with an aqueous solution of 20% potassium carbonate. Next, the organic phase is dried over anhydrous Na_2SO_4 and the solvent is removed at reduced pressure. The resulting oil is purified by silica gel column chromatography, obtaining the final product in the form of a free base. The compound is isolated in the form of a hydrochloride and purified by recrystallization. The IR and NMR spectroscopic data correspond to the free base.

(±)-2-[4-[(Chroman-2-yl)methylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 1.

Chromatography: toluene/methanol, 9:1. Yield: 35%. IR ($CHCl_3$, cm^{-1}): 1772, 1709, 1581, 1489, 1443. ^{1}H-NMR ($CDCl_3$, δ): 1.47-1.86 (m, 5H), 1.91-2.12 (m, 4H), 2.16-2.34 (m, 1H), 2.64-2.92 (m, 6H), 3.16-3.28 (m, 1H), 3.48 (t, *J* = 7.1 Hz, 2H), 3.66 (dt, *J* = 11.2; 7.3 Hz, 1H), 4.05 (dd, *J* = 9.1; 7.3 Hz, 1H), 4.11-4.18 (m, 1H), 6.81(t, *J* = 7.6 Hz, 2H), 7.00-7.10 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 24.6; 25.3; 25.8; 26.9; 27.1; 27.5; 38.7; 45.4; 49.3; 54.1; 63.2; 75.0;

116.7; 120.1; 121.9; 127.1; 129.4; 154.5; 160.8; 173.9. Analysis calculated for $C_{21}H_{24}N_2O_4S.HCl$: C, 57.72; H, 5.77; N, 6.41, found: C, 57.64; H, 5.96; N, 6.19.

EXAMPLE 2: (±)-2-[4-[(Chroman-2-yl)methylamine]butyl]-1,3-dioxoperhydroimidazo[1,5-*b*]thiazol, 2.

Chromatography: toluene/ethanol, 9.5:0.5. Yield: 43%; m.p. 149-151°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3400, 1770, 1718, 1610, 1558, 1488. ^{1}H-NMR ($CDCl_3$, δ): 1.48-1.86 (m, 5H), 2.01-2.10 (m, 1H), 2.59-3.18 (m, 9H), 3.53 (t, *J* = 7.0 Hz, 2H), 3.95-4.27 (m, 1H), 4.49 (dd, 1H, *J* = 12.0; 6.0 Hz), 5.08 (s, 1H), 6.56-6.92 (m, 2H), 7.03-7.13 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 23.9; 24.4; 25.5; 25.9; 32.7; 39.1; 48.4; 54.0; 58.3; 63.2; 74.8; 116.7; 120.0; 122.0; 127.1; 129.4; 154.6; 159.6; 171.6. Analysis calculated for $C_{19}H_{24}N_3O_3S.HCl$: C, 55.40; H, 6.36; N, 10.20, found: C, 55.38; H, 6.44; N, 9.87.

EXAMPLE 3: (±)-2-[4-[(Chroman-2-yl)methylamine]butyl]-1,3-dioxoperhydroimidazo[1,5-*c*]-thiazol, 3.

Chromatography: toluene/ethanol, 9.5:0.5. Yield: 38%; m.p. 142-144°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3400, 3500, 1770, 1716, 1582, 1540, 1508. ^{1}H-NMR ($CDCl_3$, δ): 1.49-1.74 (m, 5H), 1.98-2.05 (m, 1H), 2.60-2.84 (m, 6H), 3.12 (dd, *J* = 11.7; 5.8 Hz, 1H), 3.33 (dd, *J* = 13.5; 8.5 Hz, 1H), 3.52 (t, *J* = 7.0 Hz, 2H), 4.12 (d, *J* = 9.9 Hz, 1H), 4.22-4.28 (m, 1H), 4.33 (dd, *J* = 8.5; 5.8 Hz, 1H), 5.01 (d, *J* = 9.9 Hz, 1H), 6.77-6.88 (m, 2H), 7.04-7.13 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 23.8; 24.4; 25.6; 25.9; 32.7; 39.1; 49.2; 54.1; 58.2; 64.4; 74.2; 116.7; 120.3; 122.0; 127.1; 129.5; 154.5; 159.6; 171.9. Analysis calculated for $C_{19}H_{24}N_3O_3S.HCl$: C, 55.40; H, 6.36; N, 10.20, found: C, 55.02; H, 6.44; N, 9.85.

EXAMPLE 4: (±)-3-[4-[(Chroman-2-yl)methylamine]butyl]-2,4-

dioxothiazolidin, 4.

Chromatography: toluene/ethanol, 9.5:0.5. Yield: 45%; m.p. 126-127°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3400, 1750, 1683, 1608, 1558, 1508. ^{1}H-NMR ($CDCl_3$, δ): 1.47-1.76 (m, 5H), 2.01-2.06 (m, 1H), 2.57-3.01 (m, 6H), 3.62 (t, J = 7.2 Hz, 2H), 3.92 (s, 2H), 4.10-4.25 (m, 1H), 6.74-6.83 (m, 2H), 7.01-7.08 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 24.2; 24.5; 25.3; 25.9; 33.7; 41.8; 54.2; 58.4; 74.3; 116.7; 120.0; 122.0; 127.1; 129.5; 154.5; 171.4; 171.8. Analysis calculated for $C_{17}H_{21}N_2O_3S.HCl$: C, 55.05; H, 6.25; N, 7.55, found: C, 54.98; H, 6.33; N, 7.15.

EXAMPLE 5: (±)-3-[5-[(Chroman-2-yl)methylamine]pentyl]-2,4-dioxothiazolidin, 5.

Chromatography: toluene/ethanol, 20:1 → 8:2. Yield: 38%; m.p. 172-174°C (chloroform/ethyl acetate). IR ($CHCl_3$, cm^{-1}): 1751, 1682, 1683, 1608, 1581, 1488, 1456. ^{1}H-NMR ($CDCl_3$, δ): 1.25-2.04 (m, 8H), 2.67 (t, J = 7.0 Hz, 2H), 2.75-2.94 (m, 4H), 3.63 (t, J = 7.3 Hz, 2H), 3.92 (s, 2H), 4.08-4.17 (m, 1H), 6.78-6.85 (m, 2H), 7.01-7.11 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 24.4; 24.6; 25.7; 27.4; 29.4; 33.7; 42.0; 49.6; 54.2; 75.0; 116.7; 120.2; 122.0; 127.2; 129.5; 154.6; 171.4; 171.7. Analysis calculated for $C_{18}H_{24}N_2O_3S.HCl$: C, 56.17; H, 6.55; N, 7.28, found: C, 55.49; H, 6.49; N, 7.10.

EXAMPLE 6: (±)-3-[6-[(Chroman-2-yl)methylamine]hexyl]-2,4-dioxothiazolidin, 6.

Chromatography: toluene/ethanol, 20:1. Yield: 30%; m.p. 175-177°C (chloroform/ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3416, 3321, 1751, 1670, 1608, 1581, 1489, 1456. ^{1}H-NMR ($CDCl_3$, δ): 1.25-2.01 (m, 10H), 2.66 (t, J = 7.1 Hz, 2H), 2.76-2.95 (m, 4H), 3.62 (t, J = 7.3 Hz, 2H), 3.93 (s, 2H), 4.09-4.19 (m, 1H), 6.78-6.85 (m, 2H), 7.01-7.11 (m, 2H).

^{13}C-NMR ($CDCl_3$, δ): 24.6; 25.7; 26.6; 26.8; 27.5; 29.8; 33.7; 42.0; 49.8; 54.2; 75.1; 116.7; 120.2; 122.0; 127.2; 129.5; 154.6; 171.4; 171.7. Analysis calculated for $C_{19}H_{26}N_2O_3S.HCl$: C, 57.18; H, 6.82; N, 7.02, found: C, 56.78; H, 6.72; N, 6.94.

EXAMPLE 7: 2-[4-[(Naphth-1-yl)methylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 7.

Chromatography: ethyl acetate. Yield. 42%; m.p. 150-153°C (chloroform/hexane). IR ($CHCl_3$, cm^{-1}): 3300-3500, 1770, 1708, 1696, 1510, 1442, 1416. ^{1}H-NMR ($CDCl_3$, δ): 1.48-1.71 (m, 5H), 1.99-2.08 (m, 2H), 2.16-2.24 (m, 1H), 2.74 (t, *J* = 6.9 Hz, 2H), 3.16-3.24 (m, 1H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.64 (dt, *J* = 11.1; 7.8 Hz, 1H), 4.02 (dd, *J* = 9.3; 7.8 Hz, 1H), 4.20 (s, 2H), 7.37-7.54 (m, 4H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.82-7.85 (m, 1H), 8.08 (d, *J* = 8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, δ): 25.9; 27.0; 27.2; 27.5; 38.8; 45.5; 49.3; 51.6; 63.3; 123.6; 125.4; 125.6; 125.9; 126.1; 127.7; 128.7; 131.8; 133.9; 136.0; 160.9; 173.9. Analysis calculated for $C_{21}H_{25}N_3O_2 \cdot HCl$: C, 65.02; H, 6.76; N, 10.83, found: C, 64.53; H, 6.71; N, 10.44.

EXAMPLE 8: 2-[4-[(Naphth-2-yl)methylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 8.

Chromatography: chloroform/methanol, 9:1. Yield: 25%; m.p. 125-127°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3417, 1769, 1707. ^{1}H-NMR ($CDCl_3$, δ): 1.52-1.80, 1.92-2.23 (m, 3H), 2.80 (t, *J* = 7.1 Hz, 2H), 3.13-3.25 (m, 1H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.56-3.74 (m, 1H), 4.06-4.13 (m, 3H), 5.19 (sa, 1H), 7.45-7.50 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.78-7.92 (m, 4H). ^{13}C-NMR ($CDCl_3$, δ): 25.2; 26.8; 27.3; 29.5; 37.8; 45.3; 46.2; 51.5; 63.2; 126.3; 126.4; 126.7; 127.5; 127.8; 128.6; 129.0; 130.0; 132.9; 133.0; 160.5; 173.8. Analysis calculated for $C_{21}H_{25}N_3O_2.HCl.H_2O$: C, 62.14; H, 6.95; N, 10.35. found: C, 62.54; H, 7.06; N, 9.95.

EXAMPLE 9: 2-[4-[2-(Naphth-1-yl)ethylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 9.

Chromatography: ethyl acetate/ethanol, 1:1. Yield: 48%; m.p. 95-97°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3400 (NH), 1770, 1710. ^{1}H-NMR ($CDCl_3$, δ): 1.56-1.78 (m, 5H), 2.00-2.28 (m, 3H), 2.72 (t, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 7.1 Hz, 2H), 3.11-3.38 (m, 3H), 3.48 (t, *J* = 7.2 Hz, 2H), 3.63-3.74 (m, 1H), 4.01-4.10 (m, 1H), 7.37-7.54 (m, 4H), 7.71-7.76 (m, 1H), 7.82-7.86 (m, 1H), 7.08-7.13 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ): 27.9; 27.0; 27.1; 27.6; 33.4; 37.8; 45.5; 49.3; 50.4; 63.3; 123.7; 125.5; 125.9; 126.6; 127.0; 128.8; 132.0; 134.0; 136.0; 160.8; 174.0. Analysis calculated for $C_{22}H_{27}N_3O_2.HCl.H_2O$: C, 62.92; H, 7.20; N, 10.01, found: C, 63.40; H, 7.09; N, 9.61.

EXAMPLE 10: 3-[4-[2-(Naphth-1-yl)ethylamine]butyl]-2,4-dioxothiazolidin, 10.

Chromatography: ethyl acetate. Yield: 37%; m.p. 128-129°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 1751, 1682, 1682, 1510. ^{1}H-NMR ($CDCl_3$, δ): 1.52-1.63 (m, 4H), 2.70 (t, *J* = 6.8 Hz, 2H), 2.94 (s, 1H), 3.03 (t, *J* = 7.3 Hz, 2H), 3.32 (t, *J* = 7.6 Hz, 2H) 3.62 (t, *J* = 6.8 Hz, 2H), 3.93 (s, 2H), 7.33-7.55 (m, 4H), 7.71-7.75 (m, 1H), 7.83-7.88 (m, 1H), 8.04-8.08 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ): 25.4; 26.3; 32.7; 33.8; 41.7; 48.7; 49.9; 123.7; 125.7; 125.8; 126.1; 126.8; 127.3; 128.9; 131.0; 134.0; 135.4; 171.0; 171.5. Analysis calculated for $C_{19}H_{22}N_2O_2S$. HCl: C, 60.82; H, 6.85; N, 7.09, found: C, 62.87; H, 6.45; N, 6.90.

EXAMPLE 11: 2-[4-[2-(Naphth-2-yl)ethylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 11.

Chromatography: ethyl acetate/ethanol, 9:1. Yield: 25%; m.p. 130-132°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3421, 1769, 1705. ^{1}H-NMR ($CDCl_3$, δ): 1.59-1.89 (m, 5H), 2.03-2.27

(m, 3H), 2.98 (t, J = 7.8 Hz, 2H), 3.01-3.32 (m, 5H), 3.47 (t, J = 6.6 Hz, 2H), 3.57-3.77 (m, 1H), 4.05 (dd, J = 9.3; 7.3 Hz, 1H), 6.29 (sa, 1H), 7.32-7.48 (m, 3H), 7.68-7.80 (m, 4H). ^{13}C-NMR ($CDCl_3$, δ): 25.4; 27.1; 27.5; 31.2; 33.1; 37.9; 45.5; 47.1; 49.1; 63.4; 125.5; 125.8; 126.2; 126.9; 127.4; 127.6; 128.6; 131.8; 133.5; 139.5; 160.7; 174.1. Analysis calculated for $C_{22}H_{27}N_3O_2.HCl.H_2O$: C, 62.92; H, 7.20; N, 10.01, found: C, 63.34; H, 7.46; N, 9.65.

EXAMPLE 12: 2-[4-[2-(Phenoxy)ethylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 12.

Chromatography: toluene/ethanol, 9.5:0.5. Yield: 54%. m.p. 145-147°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3315, 1770, 1709, 1599, 1587, 1497. ^{1}H-NMR ($CDCl_3$, δ): 1.47-1.77 (m, 6H), 1.98-2.29 (m, 3H), 2.70 (t, J = 6.8 Hz, 2H), 2.99 (t, J = 4.9 Hz, 2H), 3.23 (ddd, J = 11.2; 7.6; 5.2 Hz, 1H), 3.49 (t, J = 7.3 Hz, 2H), 3.67 (dt, J = 11.2; 7.6 Hz, 1H), 4.02-4.10 (m, 3H), 6.87-6.98 (m, 3H), 7.23-7.32 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 26.0; 27.1; 27.3; 27.7; 38.9; 45.7; 48.9; 49.4; 63.4; 67.3; 114.7; 121.0; 129.6; 158.3; 160.7; 174.0. Analysis calculated for $C_{18}H_{25}N_3O_3.HCl$: C, 58.77; H, 7.12; N, 11.42, found: C, 58.79; H, 7.04; N, 11.16.

EXAMPLE 13: 3-[4-[2-(Phenoxy)ethylamine]butyl]-2,4-dioxothiazolidin, 13.

Chromatography: ethyl acetate → ethyl acetate/ethanol, 9:1. Yield: 37%; m.p. 173-174°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3413, 3327, 1751, 1685, 1599, 1587, 1497. ^{1}H-NMR ($CDCl_3$, δ): 1.48-1.72 (m, 4H), 2.70 (t, J = 7.1 Hz, 2H), 2.99 (t, J = 7.9 Hz, 2H), 3.65 (t, J = 7.1 Hz, 2H), 3.93 (s, 2H), 4.06 (t, J = 5.1 Hz, 2H), 6.88-6.98 (m, 3H), 7.23-7.32 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 25.4; 27.1; 33.7; 41.8; 48.8; 49.1; 67.1; 114.5; 120.8; 129.4; 158.8; 171.4; 171.5. Analysis calculated for $C_{15}H_{20}N_2O_3S.HCl$: C, 52.17; H, 6.14;

N, 8.12, found: C, 51.77; H, 6.04; N, 8.10.

EXAMPLE 14: 2-[4-[2-(Naphth-1-oxi)ethylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 14.

Chromatography: ethyl acetate → ethyl acetate/ethanol, 9:1. Yield: 43%; m.p. 163-164°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3354, 1771, 1707, 1582, 1508. ^{1}H-NMR ($CDCl_3$, δ): 1.58-1.77 (m, 5H), 1.93-2.30 (m, 3H), 2.86 (t, *J* = 7.1 Hz, 2H), 3.15-3.27 (m, 3H), 3.49 (t, *J* = 6.8 Hz, 2H), 3.60-3.73 (m, 1H), 4.05 (dd, *J* = 9.0; 7.3 Hz, 1H), 4.30 (t, *J* = 4.9 Hz, 2H), 6.80 (dd, *J* = 8.5; 1.2 Hz, 1H), 7.31-7.53 (m, 4H), 7.75-7.83 (m, 1H), 8.22-8.28 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ): 25.7; 26.3; 27.0; 27.5; 38.5; 45.5; 48.3; 48.8; 63.3; 66.7; 104.9; 120.6; 121.9; 125.3; 125.8; 126.4; 127.5; 125.5; 134.5; 154.3; 160.8; 174.0. Analysis calculated for $C_{22}H_{27}N_3O_3.HCl.H_2O$: C, 60.61; H, 6.94; N, 9.64, found: C, 61.00; H, 6.57; N, 9.46.

EXAMPLE 15: 3-[4-[2-(Naphth-1-oxi)ethylamine]butyl]-2,4-dioxothiazolidin, 15.

Chromatography: ethyl acetate → ethyl acetate/ethanol, 9:1. Yield: 46%; m.p. 149-151°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3332, 1684, 1582, 1508. ^{1}H-NMR ($CDCl_3$, δ): 1.58-1.70 (m, 4H), 2.81 (t, *J* = 6.8 Hz, 2H), 3.17 (t, *J* = 5.4 Hz, 2H), 3.65 (t, *J* = 6.8 Hz, 2H), 3.92 (s, 2H), 4.27 (t, *J* = 5.1 Hz, 2H), 6.81 (dd, *J* = 7.1; 1.5 Hz, 1H), 7.30-7.56 (m, 4H), 7.75-7.83 (m, 1H), 8.22-8.38 (m, 1H). ^{13}C-NMR ($CDCl_3$, δ): 25.3; 26.7; 33.7; 41.7; 48.5; 48.9; 67.1; 104.9; 120.5; 121.9; 125.2; 125.8; 126.4; 127.5; 125.6; 134.5; 154.4; 171.4; 171.5. Analysis calculated for $C_{19}H_{22}N_2O_3S.HCl$: C, 57.79; H, 5.87; N, 7.09, found: C, 57.75; H, 5.79; N, 6.59.

EXAMPLE 16: 2-[4-[(Benzimidazol-2-yl)methylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 16.

Chromatography: toluene/ethanol, 9.5:0.5. Yield: 50%; m.p.

208-210°C (ethyl acetate). IR ($CHCl_3$, cm^{-1}): 3400, 1775, 1714. ^{1}H-NMR ($CDCl_3$, δ): 1.42-1.70 (m, 5H), 1.92-2.28 (m, 3H), 2.63 (t, *J* = 6.5 Hz, 2H), 3.13-3.25 (m, 1H), 3.43 (t, *J* = 6.5 Hz, 2H), 3.55-3.64 (m, 1H), 4.00 (m, 2H), 7.10-7.18 (m, 2H), 7.47-7.53 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 25.4; 26.2; 27.0; 27.5; 38.4; 45.4; 47.6; 48.5; 63.3; 115.0; 122.0; 139.0; 154.0; 160.8; 174.0.

EXAMPLE 17: 2-[4-[(*o*-Methoxyphenyl)methylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 17.

Chromatography: ethyl acetate/hexane. Yield: 42%; oil. IR ($CHCl_3$, cm^{-1}): 3016-2837, 1770, 1706, 1600, 1492, 1442, 1415, 1242. ^{1}H-NMR ($CDCl_3$, δ): 1.47-1.72 (m, 3H), 1.95-2.09 (m, 2H), 2.17-2.28 (m, 1H), 2.59 (t, *J* = 7.1 Hz, 2H), 3.18-3.26 (m, 1H), 3.45 (t, *J* = 7.1 Hz, 2H), 3.65 (dt, *J* = 11.1; 7.9 Hz, 1H), 3.76 (s, 2H), 3.82 (s, 3H), 4.04 (dd, *J* = 9.3; 7.9 Hz, 1H), 6.83-6.91 (m, 2H), 7.20-7.25 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 24.4; 26.0; 27.0; 27.5; 38.9; 45.5; 47.1; 53.3; 63.3; 110.1; 120.3; 127.1; 130.3; 157.5; 160.9; 174.0. Analysis calculated for $C_{18}H_{24}N_3O_3 \cdot HCl.3/2.H_2O$: C, 54.88; H, 7.16; N, 10.67, found: C, 54.52; H, 7.09; N, 10.52.

EXAMPLE 18: 2-[4-[2-(*o*-Methoxyphenyl)ethylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 18.

Chromatography: ethyl acetate/hexane. Yield. 25%; m.p. 160-162°C (chloroform/hexane). IR ($CHCl_3$, cm^{-1}): 3018-2899, 1770, 1709, 1495, 1443, 1418, 1244. ^{1}H-NMR ($CDCl_3$, δ): 1.60-1.77 (m, 5H), 1.96-2.27 (m, 3H), 2.75 (t, *J* = 6.8 Hz, 2H), 2.92 (s, 4H), 3.15-3.27 (m, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.65 (dt, *J* = 11.0; 7.6 Hz, 1H), 3.79 (s, 3H), 4.05 (dd, *J* = 9.0; 7.3 Hz, 1H), 4.62 (sa, 1H), 6.80-6.89 (m, 2H), 7.13-7.22 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 25.6; 27.0; 27.5; 27.5; 29.7; 38.4; 45.5; 48.3; 48.7; 55.2; 63.3; 110.3; 120.5; 127.2; 127.7; 130.4; 157.5; 160.7; 173.9.

Analysis calculated for $C_{19}H_{26}N_3O_3 \cdot HCl.H_2O$: C, 57.20; H, 7.33; N, 10.53, found: C, 57.43; H, 7.03; N, 10.41.

EXAMPLE 19: 2-[4-[3-(*o*-Methoxyphenyl)propylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 19.

Chromatography: toluene/methanol. Yield: 52%; oil. IR ($CHCl_3$, cm^{-1}): 3018-2700, 1772, 1709, 1492, 1442, 1418, 1244. ^{1}H-NMR ($CDCl_3$, δ): 1.60-1.81 (m, 5H), 1.93-2.34 (m, 5H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.77 (m, 4H), 3.16-3.28 (m, 1H), 3.46 (t, *J* = 6.6 Hz), 3.67 (dt, *J* = 11.1; 7.6 Hz, 1H), 3.75 (s, 3H), 4.07 (dd, *J* = 9.3; 7.3 Hz, 1H), 6.81-6.90 (m, 2H), 7.10-7.21 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 24.9; 25.6; 27.1; 27.5; 27.6; 27.9; 38.3; 45.6; 48.1; 48.4; 55.4; 63.4; 110.4; 120.6; 127.4; 129.3; 130.0; 157.4; 160.8; 174.0. Analysis calculated for $C_{20}H_{28}N_3O_3 \cdot HCl.3/2H_2O$: C, 56.93; H, 7.64; N, 9.93, found: C, 57.23; H, 7.21; N, 9.40.

EXAMPLE 20: 2-[4-[4-(*o*-Methoxyphenyl)butylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 20.

Chromatography: chloroform/methanol, 9.5:0.5. Yield: 27% (oil). IR ($CHCl_3$, cm^{-1}): 3700, 1770, 1709, 1601, 1443, 1495, 1585, 1215. ^{1}H-NMR ($CDCl_3$, δ): 1.58-1.74 (m, 9H), 2.01-2.11 (m, 2H), 2.17-2.27 (m, 1H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.65-2.570 (m, 4H), 3.18-3.26 (m, 1H), 3.46 (t, *J* = 6.8 Hz, 2H), 3.66 (dt, *J* = 11.2; 7.6 Hz, 1H), 3.79 (s, 3H), 4.05 (dd, *J* = 9.0; 7.6 Hz, 1H), 6.80-6.87 (m, 2H), 7.09-7.17 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 23.4; 25.2; 26.3; 27.0; 27.4; 29.6; 37.8; 45.4; 47.1; 47.8; 55.1; 63.4; 110.1; 120.3; 127.1; 129.7; 129.9; 157.2; 160.6; 173.9. Analysis calculated for $C_{21}H_{31}N_3O_3.HCl.3/2H_2O$: C, 60.31; H, 7.95; N, 10.05, found: C, 60.70; H, 7.56; N, 9.77.

EXAMPLE 21: 2-[3-[3-(*o*-Methoxyphenyl)propylamine]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazol, 21.

Chromatography: chloroform/methanol, 9.5:0.5. Yield: 27% (oil). IR ($CHCl_3$, cm^{-1}): 3700, 1770, 1707, 1601, 1587, 1493,

1445, 1215. ^{1}H-NMR ($CDCl_3$, δ): 1.62-1.86 (m, 5H), 2.02-2.32 (m, 3H), 2.56-2.67 (m, 6H), 3.24 (m, 1H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.67 (dt, *J* = 11.2; 7.6 Hz, 1H), 3.81 (s, 3H), 4.06 (dd, *J* = 9.0; 7.3 Hz, 1H), 6.81-6.91 (m, 2H), 7.10-7.22 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 26.9; 27.5; 27.8; 28.4; 30.0; 36.9; 45.5; 46.7; 49.5; 55.2; 63.3; 110.2; 120.3; 127.0; 129.8; 130.5; 157.4; 160.9; 174.0. Analysis calculated for $C_{18}H_{25}N_3O_3.HCl.3H_2O$: C, 51.24; H, 7.64; N, 9.96, found: C, 51.26; H, 7.25; N, 9.57.

EXAMPLE 22: Determination of the receptor affinity.

Biochemical studies to determine the affinity of synthesized compounds have been carried out by radioligand displacement experiments, experiments being carried out to determine the receptor affinity for the 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, 5-HT_4, 5-HT_7, α_1 and D_2 receptors.

The conditions for each receptor studied is summarized in Table 1 below, while the receptor affinity data is summarized in Table 2 below.

TABLE 1 (separately enclosed)

TABLE 2 (separately enclosed)

EXAMPLE 23: *In vitro* functional characterization.

The functional character of the new compounds was initially determined by studying their effect on adenylate cyclase in He-La cells transfected with the 5-human HT_{1A} receptor, measuring their inhibiting effect on the stimulation of the enzyme induced by forskolin (Table 3 below). The compounds included in this table behaved in all cases as pure agonists, so as to reach values close to 100% of inhibition of the activation induced by forskolin. The 50 effective concentration (CE_{50}), a concentration that produces 50% of the inhibition of the increase in enzymatic activity by forskolin, was in the nanomolar range. The action of the new compounds in this test was mediated in by the 5-HT_{1A} receptor as can be deduced from the blocking of the effect of all compounds studied by the selective 5-HT_{1A} antagonist WAY-100635 (10^{-8} M).

TABLE 3. Test on adenylate cyclase in He-La cells

Compound no.	CE_{50} (nM)	% Maximum inhibition
1	16.3	94.6
2	18.9	94.5
3	31.5	89.3
4	11.6	89.6
12	76.2	87.4

The *in vitro* agonist character of the new compounds was also evaluated in some cases by the fixation test of [^{35}S]-GTPγS to coronal sections of rat brain. In this test, the results obtained with compounds no. 1 and no. 3, at a concentration of 10 μM, were especially similar to those obtained with the 5-HT_{1A}, 8-OH-DPAT agonist prototype. In the autoradiograms, an increase in intensity of the signal in the hippocampus (CA1, CA2, CA3 and dentate gyrus),

thalamic nuclei, amygdaloid complex, cortex and in the mediobasal hypothalamus nuclei was observed. The increase in intensity of the marking in these cerebral areas was reduced until reaching control levels when the incubation was carried out in the presence of both the molecule under study and the selective 5-HT_{1A} antagonist WAY-100635 (1 µM).

The five compounds included in Table 3 likewise produced hyperpolarization of the potential of the neurons of the hippocampal area CA1. By carrying out dose-effect curves, it was observed that the action of compounds no. 1 and no. 2 in this test was indistinguishable in potency to that of the 5-HT_{1A}, 8-OH-DPAT type agonist.

EXAMPLE 24: *In vivo* functional characterization.

All compounds previously characterized *in vitro* as 5-HT_{1A} agonists (Table 3) were delivered by subcutaneous injection to mice in order to quantify the hypothermia associated to stimulation of this serotonergic receptor subtype. In all cases, a reduction in the rectal temperature of the mouse was observed of a variable duration ranging from between 30 and 120 minutes. In Table 4 below, the minimum effective doses for each compound studied and the degree of hypothermia reached at this dose are shown. The maximum hypothermic effect was reached with doses 4-8 times higher than those indicated in this Table 4, in some cases reaching temperature decreases of 4°C.

TABLE 4. Mouse hypothermia test

Compound no.	Minimum effective dosage (mg/kg)	Hypothermic effect (°C)
1	2.5	1.4
2	1.25	1.5
3	1.25	1.3

4	0.3	2.0
12	2.5	1.4

EXAMPLE 25: Determination of the *in vitro* neuroprotective action.

The neuroprotective effect of the compounds considered was studied in experimental models *in vitro*, using primary cultures of rat hippocampus exposed to serum deprivation, to a toxic concentration of glutamate, or incubated in conditions of hypoxia and absence of glucose.

In the model of apoptotic neuronal death induced by incubation of mixed cultures of neurons and glial cells for 24 hours in a medium without serum, the neuroprotective effect of compound no. 1 is to be highlighted, with which a concentration-dependent effect was observed which was even higher (more than 40% protection) than that obtained with the 8-OH-DPAT agonist. Other compounds were also shown to be effective such as no. 4 and no. 12, although in both cases the degree of protection was somewhat below at the various concentrations used in the tests.

In the model of excitotoxic neuronal death due to exposure of the neuronal cultures to 1mM glutamate, compound 1 was that which most effectively prevented (37%) the associated damage. Likewise, this compound showed a neuroprotective effect (> 20%) in the model of neuronal death due to exposure of the cultures to a transient hypoxia situation in the absence of glucose and subsequent incubation in a 5% CO_2 atmosphere.

EXAMPLE 26: Determination of the *in vivo* neuroprotective action.

The *in vivo* neuroprotective action was evaluated both in the transient global ischemia model in gerbils and in the permanent focal ischemia model in rats.

In the transient ischemia model in gerbils induced by

temporary occlusion of both carotid arteries, the delivery of compounds no. 1 and no. 12, 30 minutes before the induction of the ischemia, and 24 and 48 hours afterwards, significantly prevented the injury induced by the ischemic process in the hippocampal area CA1, which was evaluated by Nissl stain. The neuroprotective effect was dose-dependent, between 1-5 mg/kg by subcutaneous injection, reaching, with compound no. 1, a degree of total protection of the injury in approximately half the animals at a dose of 5 mg/kg. This protection was accompanied by a hypothermic effect, likewise dependent on the dose delivered.

In the focal ischemia model due to permanent occlusion of the middle cerebral artery in the rat, the delivery of compound no. 1 by intravenous injection, 45 minutes before and 45 minutes after the occlusion, significantly reduced the volume of the infarcted area. Specifically, at a dose of 2 mg/kg, the infarction volume was reduced by more than 25%.